A STUDY OF SOME OF THE DRUGS USED IN FUNCTIONAL NERVOUS DISORDERS.[1]

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FIRST PAPER.

IN the treatment of functional nervous disorders, as in other fields, there is a great temptation to secure rapid and striking results. Methods and agents that accomplish them are eagerly adopted by the profession; while others, less attractive, naturally fall into disuse. It is not strange, therefore, that, in the continual looking to immediate effects, there is a disposition to give secondary consideration to the means employed, and too often to forget the rigid scrutiny to which they should be subjected.

The purpose of this paper is to call attention to the general character of the methods in vogue, and to discuss in detail the nature and mode of action of a few of the drugs that are used to-day.

There are two things that impress the student of therapeutics as applied to functional nervous disorders: First, the necessity for pushing familiar drugs to their physiological limits; second, the large number of new drugs reported as accomplishing startling results without a sequence of dangerous or unpleasant symptoms. It is not unreasonable to suspect that such reports are based on insufficient data, and that better acquaintance with these drugs will reveal elements no less dangerous, because insidious. The fact that they are effective in many obstinate conditions, places them in the category of drugs of profound action. The hiatus between the physiology of a drug and its therapeutic application is always great, but much can be done toward bridging it over by a careful study of some special disease, in which the symptoms are marked, and over which the drug is found to have control. Such a study will be of value, not only in placing the drug where it belongs, but also in guarding the physician against its abuse. There is the greater need for caution in the treatment of functional nervous disorders; for, in the absence of organic disease, alarming symptoms are slow to arise, and are often to be found only as a general depression of the forces, whether physical or mental.

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As we have just seen, the main reliance in the treatment of functional nervous diseases to-day is on some drugs in excessive doses, and on others having profound effects. Our study is made easier by that fact, since we are warranted in drawing some information from positive lesions, the result of toxic doses of the drugs in question.

Your attention is directed, first, to the drugs used in chorea. First and foremost among them stands arsenic. Its physiology and toxicology are too well known to require even a review. For the sake of emphasis, however, certain points will be mentioned.

In small doses, arsenic is a tonic. It is rapidly absorbed, and appears to act directly over the tissues with which it comes in contact, by irritating the end organs of the nerves supplying those parts. It increases the appetite, the glycogenic function of the liver, and the excretory functions. It increases the action of the heart, and raises the blood pressure, both by its action on the heart and on the vaso-motor system. It increases the number of red blood corpuscles, diminishes the absorption of oxygen, and the evolution of carbonic acid, and checks retrograde metamorphosis. It stimulates respiration, and it increases the general tone of the muscular system.

All this is true when the drug is given in small doses and for a short period.

In toxic doses, arsenic acts as a powerful gastro-intestinal irritant. It paralyzes the end organs in the vaso-motor system, decomposes the hæmoglobin of the blood, and renders it less coagulable. Motor and sensory disturbances are common. In the one hundred cases of poisoning reported by Joubert Gourbeyre (" Des Suites de l'Empoisonnement Arsenicale," Paris, 1881), seventy-five had hemiplegia or local palsy, twenty-five paraplegia. Symptoms in many cases resemble those of multiple neuritis or sub-acute poliomyelitis. Sklarek and Ringer and Murrell, in their experiments on frogs, found that sensation and motion were abolished by the action of the drug on the spinal centres.

The effects of full medicinal doses long continued are in many respects similar to the toxic. There is a decrease in the red blood corpuscles, decomposition of the hæmoglobin, and diminished coagulative power—œdema, of the eyelids, general œdema, albuminuria. The heart's action is feeble and irritable, the blood pressure diminished; the temperature is lowered, breathing oppressed, and motility and sensibility affected. In many cases the first symptom is a multiple neuritis, a herpes zoster, or a pigmentation of the skin.

It is not necessary to dwell on these symptoms of chronic poisoning; every one knows them, and avoids them as far as he is able.

There is, however, a large class of patients who have been taking moderately small doses of arsenic, from six months up, in whom are to be found few, if any, of the symptoms mentioned above, but who bear characteristic marks of their treatment. The skin is pale, often sallow to the point of muddiness; the air is languid, the gait rather uncertain, the hands moist, flesh flabby, appetite poor, habit constipated, heart's action feeble (frequently accompanied with palpitation or irregularity), pulse soft, respiration shallow. Examination of the muscular system reveals a lack of tone. This can be done with accuracy in the case of the extrinsic muscles of the eyes, the examination of which has been reduced to a science. They are found to be in a weak state bordering on paresis. With an esophoria of high degree, the nasal rotation is poor; with an exophoria, the temporal rotation is imperfect; abduction and adduction are usually limited. In general, the condition of the patient is what might be called below par.

Although many of these symptoms cannot have gone unnoticed by any one who has systematically prescribed arsenic, little mention is made of them. A notable exception is Dr. J. Hutchinson, who, in several monographs, calls attention to the effects of long-continued use of the drug. In the *Archives of Surgery*, London, 1889, he says: "My experience in the medicinal use of arsenic has been very considerable, and my impressions regarding its effects, when long continued, are certainly very different from what we have recently seen so freely expressed. I never knew a patient to become fond of arsenic or experience agreeable effects from its long continuance. On the contrary, nothing but anxiety to be rid of a loathsome skin disease will induce the majority of those for whom it is prescribed to continue taking it. Its general effect, if pushed, is not to give vigor, but to diminish it, and make the patient feel apathetic and uncomfortable. So far from its usual effects being to clear the complexion, I believe that, unless the dose be very small, it not unfrequently makes the skin dry and earthy and the eye dull. Patients who have taken arsenic for long periods are, I think, without exception, glad to leave it off, and always experience improvement in general health when they do so. In very small doses it may have some tonic influence, but I do not think it is one that patients can appreciate."

Among its therapeutic effects the influence of arsenic upon chorea is considered one of the most important. That it will, in many cases, stop choreic twitchings, no one will deny. By what means it accomplishes this, every therapeutist confesses that he is ignorant. Wood has decided that it acts in "some unknown way," and most authors admit as much. Hutchinson goes so far as to say: "That arsenic has a special affinity for nerve-tissue, and some peculiar influence on nerve-function, we may safely believe; but further than this we can scarcely go." Scientifically perhaps we do not know, but practically there would not seem to be occasion for so much hesitation. Let us see what data we have upon which to base an opinion. In the first place, it will be admitted that the essential thing in chorea is involuntary muscular contraction. To affect this, one of three things is necessary: To remove the cause; to produce anæsthesia of the afferent, or paralysis of the efferent nerves, or affect the conductivity of the cord. We have seen that in doses such as are prescribed for chorea, there is a decomposition of the blood and an increase in retrograde metamorphosis. In toxic doses there is usually a degenerative change in the spinal cord. Brunton has shown that the irritability of a muscle is not affected by arsenic, but that the work which it can do is diminished. It is probable, therefore, that the action of arsenic in chorea is twofold: Primarily a depression of the spinal centres by reason of the poverty of the blood; in the second case, and to a much less degree, a reduction of the working power of the muscles by the direct effect of the drug.

The next drug to which your attention is directed is chloral. The physiological effects are a powerful and certain hypnotic by its action on the cerebrum. When continued for a long time, the symptoms are sleeplessness, great mental irritability and muscular prostration, uncertainty of movements, with tendency to fall forward, appetite capricious, and frequent nausea; injection of the conjunctiva with yellowness. The direct effect on the muscles is to reduce the excitability as well as their working power. General symptoms of purpura; surface of body, especially on the back and fore part of the chest, is covered with reddish brown patches.

In regard to the use of chloral for the relief of chorea, there is little to be said. The cases in which it has proved of most value are those of acute and violent chorea, where an immediate cessation of spasm is requisite to the safety of the patient. Here the hypnotic effect of the drug is pushed to the point of producing coma, and the patient kept under its influence until the nervous centres have had time to regain their lost equilibrium. The theory for its use was the fact that in sleep choreic movements usually cease. Chloral was quoted as a pure hypnotic. What could be a more ideal course of treatment than to maintain a natural sleep until the tendency to relapse should pass! Many satisfactory results have been reported. The large amount of chloral required in such and similar cases, however, to produce sleep, certainly creates a doubt in the mind whether the effect is produced through the hypnotic action of the drug so much as by the profound depression of the brain and spinal centres and direct action on the muscles themselves. More will be said of chloral and its action when the subject of insomnia is reached.

Some attention has been directed of late to the use of antipyretics in chorea. These drugs, on their introduction into the pharmacopœia, met with a most cordial, not to say, eager reception, and they are now enjoying almost unlimited freedom, because their administration is pleasant, their work rapid, and their employment attended with no alarming symptoms. There is no reason to doubt, however, that, like many of their predecessors that have accomplished great results with little display, they may have dangerous properties concealed. The very fact that they may be able to affect disorders of the character of chorea lays them open to suspicion, while it half suggests the nature of their action. Indeed, a reaction is already finding expression in the distrust shown among therapeutists for their effect in fevers—that field in which their value seemed most promising. So that when Dr. Masins, at the International Congress of Therapeutics and Materia Medica, held in Paris, 1890, affirmed their value in all febrile diseases, he was met by a general expression of dissent. Dr. Williams, of Boston, condemned their use because they seldom benefited the disease, and their result was to retard convalescence. Dr. Stockwin held them as little better than poisons; and in Dr. Semnala's opinion they give temporary relief only at the expense of the patient's strength.

Their most prominent feature is their power to reduce bodily temperature. Experimental research has led the majority of physiologists to the conclusion that this is due to the action of the drug on the thermogenic centres in the brain. They regard other effects of secondary importance. Of these observers, Ott, Girard, Cerne and Carter agree that antipyrine has no effect on the blood except in excessive doses. Batten and Bokenham, quoted by Ott, found that antipyrine acts upon all parts of the nervous system, mainly the spinal cord, but also on the brain and motor nerves, the symptoms produced being similar to those seen in lateral sclerosis. It causes tetanic convulsions; and the subsequent paralysis of the nerve centres is followed by a disappearance of reflex excitability. If directly injected into a muscle, it loses its excitability. It depresses the sensory centres. In small doses it acts as a cardio-motor stimulant, and in large doses, a cardiac depressant and a dilator of the capillaries.

The conclusion in regard to heat-reduction, arrived at by the investigators mentioned above, is open to some criticism; and Illingworth (*Provincial Medical Journal*, January, 1892) says very pertinently of Girard's experiments: "It is no proof that because antipyrine exerts its antipyretic effect while Dr. Girard is making his experiments on the striate body that the drug is necessarily operating on the same centre. It is much more in accordance with the symptoms observed in the administration of the drug to aver that it acts primarily on the red blood corpuscles, partially to prevent the oxygenation of the hæmoglobin. This action of the drug on the blood has a rapid effect on the heart, reducing the strength of the pulsations, and thus upon the respiration, which becomes slower. The deficient oxygenation will have the effect also of diminishing the fibrin-forming power of the blood." In support of this, he shows that antipyrine added to freshly-drawn blood dissolves out the hæmoglobin, deprives the corpuscles of their color and their tendency to form *rouleaux*. Each corpuscle, much reduced in size, stands distinct from the rest and absolutely destitute of viscidity. The effect on a blood clot is to clarify and soften it. "It is evident, therefore, that in common with many drugs, but in a much more marked and wonderful manner, this drug liquifies the blood by diminishing its fibrin-forming power." He says, further, that the analgesic effects of the drug are due directly to this liquefacient property. By increasing the circulation, the tension in congested parts is reduced and the pain relieved. To this action he attributes its efficacy in migraine.

Should the opinions of this observer prove correct their importance cannot be over-estimated. It would establish another bond of similarity between antipyrine and its congeners—phenacetine and exalgine. It has been observed that the latter drugs have a decided effect on the blood to change the hæmoglobin to methæglobin. It is worthy of note, also, that, as Dujardin-Beaumetz has shown, the analgesic properties of the different antipyretics are in proportion to their power to change hæmoglobin into methæmoglobin. It would greatly elucidate the action of the antipyretics in widely different diseases should it be proven that the first effect of these drugs is on the blood, and the depression of the thermogenic centres a result of the poverty of the blood.

Whether the primary effect of antipyrine is upon the blood or not will concern the neurologist but little, since in such conditions as chorea it must be prescribed in sufficiently large doses to produce a marked lessening of muscular contractions, and in such doses it certainly causes changes in the blood.

The manner in which antipyrine arrests chorea evolves itself from the foregoing. In the present state of our knowledge a positive opinion is not possible. It may be conjectured, however, that there is a decrease in the excitability of the muscles themselves by the direct action of the drug, and the sensory centres in the spinal cord depressed by degenerative changes in the blood.

Thus it is seen that in all of the drugs that have won reputation in the treatment of chorea, the feature of most prominence is their power to cause a depression of sensation and motion to the point of paralysis; that in doses short of this effect they are not of much value; and, finally, that when they are administered in doses sufficient to check choreic movements, other systemic effects, such as general depletion of the forces of the body, degeneration of the blood, vascular dilatation, and cardiac and respiratory depression, attend their specific action.

Let us turn now from chorea to a disorder in which cerebral symptoms are more marked. One of the distressing conditions that the neurologist is frequently called upon to treat, and one that often proves obstinate, is insomnia. Whether it occurs as a symptom complicating other conditions, or whether it is the only thing for which the patient seeks relief, its persistence is characteristic.

The drugs that have proved most efficacious in producing sleep are chloral and sulphonal. When the insomnia is recent, or the result of temporary irritations, the drugs induce sleep, and may be prescribed as indicated. When, on the other hand, the insomnia is chronic, particularly that form which is frequently referred to as the forerunner of insanity, the protracted use of hypnotics is not attended with that perfect immunity from unpleasant effects, that almost all the reports on the subject would lead us to expect. Reference is not here made to the toxic effects of either drug, but rather to those effects that are likely to escape attention, and in many cases come to be regarded as belonging to the insomnia itself.

To attempt to explain the manner in which the so-called pure hypnotics produce their effects would be to explain the physiology of sleep, and the result would not be satisfactory. It may be well, however, to take exception to the term pure hypnotic until we know in what sleep consists. The most that can be said of the hypnotics is that they produce unconsciousness, in which the respiration, the pulse, and the temperature are those of natural sleep. This is far from saying that they produce natural sleep. No one who has seen the violence of mania, or the spasms of chorea, give way under the use of chloral, can reasonably believe that the drug has induced a physiological condition; and yet, to read the reports of the men who have employed the drug in such cases, you would imagine that they were dealing with a perfectly harmless drug. If chloral were a pure hypnotic there would not be such a short step from the "calm, quiet sleep," caused by it, to the profound coma and the paralysis of the heart and respiration. As a matter of fact the effects of chloral mentioned in connection with chorea go far to show that the unconsciousness of chloral is as far removed as possible from natural sleep.

The large number of persons suffering from insomnia who find their way to the specialist demonstrate only too frequently the failure of the hypnotics to accomplish what was expected of them, and that too in the hands of the skilled general practitioner who has used the drugs judiciously. They comprise two classes: those who are taking chloral or sulphonal yet cannot sleep; and those who sleep when they take the drug, but consult you for "extreme nervousness." These people have certain traits in common. The first thing that attracts your attention is the hard set features, the fixed look, the dull, heavy eyes, often congested, the dusky pallor of the complexion, the expression of despair. However infectious the mirth about them, the face never relaxes in a smile. The patient walks as if in a trance, and talks in an automatic manner; he knows that his words are producing no effect, and when ignored, accepts the fact without emotion. The mental conditions differ somewhat in chloral and sulphonal. In the former there is more excitement and irritability; in the latter, more despair; but in both there is the hopeless wail over their condition, irrational harping on their symptoms, and what may be called a mental vacuity for other topics. The disturbances of motility are not usually sufficient to attract attention, although in some cases trembling is observed. Dr. Stevens has called my attention to a peculiar effect of chloral on the ocular muscles. If in normal conditions daily tests of the eyes of the same individual are made, it will be found that there is a constant relation between the tests of consecutive days. That is, with a certain amount of exophoria or esophoria there is a certain amount of abduction. There may be esophoria with excessive abduction, or exophoria with deficient abduction; but with every change in the esophoria or exophoria there is a corresponding change in the abduction. Right hyperphoria remains right hyperphoria, and left hyperphoria left hyperphoria. In many patients who are taking chloral this relation is constantly changing. A sort of insanity of the muscles exists, and it is absolutely impossible to arrive at any knowledge of the relation of the eyes. This effect is so characteristic that not unfrequently it has been the first information given by the patient that he was in the habit of taking sleeping powders.

That the effects mentioned above are caused by the hypnotic and are not a part of the insomnia may be readily demonstrated by removing the drug. It is remarkable what a change a few days' relief from the drug will produce. To suggest such a course to the patient is usually to call forth wild assurances that he will go mad without it. However, if he has the belief impressed upon him that a few nights' sleep are not necessary to his existence and sanity, he will generally acquiesce. He will not sleep as much as usual, perhaps, but it will be gratifiying to observe the softening of that hard expression, certainly a better complexion, it may be a faint smile of surprise that he is not so much worse off than before, and a return to a somewhat normal state of mind in which he can discuss his condition in a more rational manner. The trembling of the hands and head will cease, and the action of the ocular muscles become regular.

These effects follow immediately on the removal of the drug. What seems to be the direct cerebral effects of the hypnotic are not so easy of dissipation, and it is sometimes weeks or months before those attacks of unreasoning complaints cease to occur. A complete removal of all depressing drugs, and a course of treatment essentially tonic, will, as a rule, accomplish this, and a strengthening of the general system will eradicate many of the unpleasant symptoms attending insomnia.

To prevent repetition and avoid unnecessary prolonging of this paper, sulphonal and chloral have been considered together. That the physiology of the two drugs is in many respects radically different is fully recognized. As employed in the treatment of insomnia, however, the manifestations of their cerebral effects reveal much similarity in action. Sulphonal deserves some special mention from the fact that all the reports of the drug found in our journals are surprisingly flattering. Thus, Burnett (*Kan. City Med. Index*, 1891, xii., 289) says: "As a hypnotic, under all circumstances, when judiciously prescribed, it certainly stands at the head of the list in producing a refreshing, quiet, physiological sleep, without a systemic reaction which invariably follows all other hypnotics in degree." But when he says, later: "To hope for improvement in any neurotic patient necessitates as near as possible the establishment of physiological equilibrium of that nervous system, and to do this an avoidance of all extremes must be adhered to;" and when he confesses that in insanity sulphonal seems to him almost a supernatural gift, his first statement loses force.

J. Carlyle Johnstone (*Jour. Mental Science*, London, 1892) reports favorably on the drug, and sums up by saying that it has no injurious effects on the circulation, respiration, appetite, digestion, temperature, or on the general health. And yet immediately afterward he says, that its action is continued until the next day and followed by drowsiness, confusion, giddiness or fatigue; serious cerebral and motor symptoms are apt to follow repeated doses. Gordon (*Brit. Med. Jour.*, 1890) reports favorably, but observes, in passing, that in waking from their sleep many patients show great confusion, being unable to tell who they are and where they are.

It is quite natural that the man in whose hands a new drug has given satisfactory results should be the one who makes a report of the drug. Successes are easy to report. But the man who fails in his efforts does not, as a rule, rush into print with them, and much valuable information in regard to the therapeutic effects of the drug is lost. In the second place, when a physician prescribes a drug for a malady, his attention is directed so much to the effect of the drug on the disease itself, that the other systemic effects are apt to be disregarded, unless they assume alarming proportions. The reports based on such therapeutic experiments are consequently one-sided, and statements of the innocuous properties of the drug in question are not well founded.

Daily contact with patients who have taken these drugs for varying periods of time has forced upon me conclusions that go far from supporting the opinions commonly expressed. This is so true that a large number of patients who present themselves for treatment will be found to be suffering as much from the drugs they have been taking as from the original disorder, and an absolute removal of all drugs will serve not only to elucidate the condition, but frequently also to give much relief to the sufferer.

A discussion of the drugs used in headache and epilepsy must be reserved for a future paper.

Sufficient has been said, however, to raise a suggestion that drugs which produce marked effects in functional nervous disorders are themselves subject to suspicion and should be studied with as much care as there is of eagerness displayed in effecting a cure of the disease.

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